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Neutrophilic asthma has different radiographic features to COPD and smokers

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KEYWORDS

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Summary

Background: Neutrophilic asthma and COPD are obstructive airway diseases common in older age and have a characteristic airway inflammation with neutrophilic bronchitis. The structural differences between neutrophilic asthma and COPD have not been investigated. The aim of this study was to examine the airway and parenchymal abnormalities using high resolution computed tomographic (HRCT) scanning in participants with neutrophilic asthma, COPD and smoking controls.

Methods: Participants (neutrophilic asthma ($n = 10$), COPD ($n = 17$) and smoking controls ($n = 8$)) underwent clinical assessment and sputum induction. HRCT of the chest was performed and independently scored by a radiologist blinded to the subject group using a modified Bhalla scoring system.

Results: Participants were of a similar age and those with COPD had a similar degree of airflow obstruction to those with neutrophilic asthma. The pattern of radiographic abnormalities differed between groups. Abnormal bronchial wall thickening was significantly more common in neutrophilic asthma, compared to COPD or smoking controls. Emphysema was greatest in the COPD group, and not recorded as a feature of neutrophilic asthma. FEV₁% predicted was negatively associated with bronchial wall thickening and consolidation while KCO% predicted was negatively associated with the total emphysema score. Bronchiectasis was minimal in all groups.

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity; HRCT, High resolution computed tomography; ICS, Inhaled corticosteroids; NA, Neutrophilic asthma; SC, Smoking controls; TCC, Total cell count.

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Conclusion: The pattern of radiographic lung abnormality in neutrophilic asthma differs significantly from COPD, and resembles asthma. Neutrophilic asthma is a distinct inflammatory subtype of asthma with a different pathogenesis to COPD.

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Introduction

Asthma is an obstructive airway disease characterised by an abnormal and heterogeneous airway inflammatory response. In addition to the allergen driven, corticosteroid sensitive eosinophilic pattern, many patients exhibit a noneosinophilic form of the disease that is relatively resistant to inhaled corticosteroid therapy.^{1–3} Neutrophilic asthma (NA) is present in about 20–30% of asthmatics and is characterised by an intense neutrophilic bronchitis and dysfunction of the innate immune system.⁴ The consequences of this response may be airway wall remodelling. Remodelling is well described with eosinophilic airway inflammation,⁵ where the changes can be detected by high resolution computed tomographic (HRCT) scanning and include bronchial wall thickening, mosaic lung attenuation, and mucus plugging.^{6,7} It is unclear if there are structural airway changes in neutrophilic asthma.

Chronic Obstructive Pulmonary Disease (COPD) is an obstructive and inflammatory airway disease typically with increased neutrophils and like NA; it is more common in older people. COPD is accompanied by well-established structural pulmonary changes. Typically this is emphysema, but bronchiectasis and bronchial wall thickening have recently been recognised to occur in COPD.^{8,9} Since there are similarities in the demographic profile and inflammatory response between NA and COPD, it has been suggested that NA may be a form of COPD. If this was the case, then there would be similar structural changes in NA and COPD.

The purpose of this study was to examine pulmonary airway and parenchymal changes in NA and COPD using HRCT of the chest. Since smoking can modify the inflammatory response, a group of smoking controls without known airway disease were included for comparison. We tested the hypothesis that NA was associated with a distinctly different pattern of HRCT abnormality to COPD and smoking controls.

Methods

Participants

Participants with NA ($n = 10$), COPD ($n = 17$) and smokers without diagnosed airway disease (SC; $n = 8$) were recruited from the Ambulatory Care Service at John Hunter Hospital and by advertisement (SC). The participants with NA and COPD had stable symptoms and treatment, and no exacerbation or treatment changes in the 4 weeks prior to enrolment in the study. The participants with NA met American Thoracic Society criteria for asthma diagnosis¹⁰ and had current asthma symptoms, airway hyper-responsiveness to 4.5% saline, and increased sputum neutrophil counts ($>61\%$).¹ The participants with COPD had

incomplete reversibility of airflow obstruction with post-bronchodilator $FEV_1 < 80\%$ predicted and FEV_1/VC ratio < 0.7 .¹¹ They had no history of asthma and a significant past smoking history. The smoker controls were current or exsmokers with no diagnosed respiratory disease, no treatment and no airflow obstruction. All participants were stable (no lower respiratory tract infection or exacerbation of respiratory disease in the previous 4 weeks) at the time of assessment.

Design

Participants attended for 2 study visits. At the first visit, written informed consent was obtained followed by clinical assessment, spirometry, gas diffusion studies, combined hypertonic saline challenge and sputum induction as well as a skin allergy test. Participants then attended a second visit for chest HRCT. The Hunter Area Health Service and The University of Newcastle Research Ethics Committees approved this study.

Chest CT

HRCT of the chest was obtained using Cardiac 64 multislice scanner (Siemens, Germany). Sections of 1 mm thicknesses were obtained at 10 mm intervals in full inspiration and in expiration. A high spatial resolution algorithm was used and images were photographed at appropriate window settings (lung window: level -700 HU; window 2000 HU). Scans were scored independently by a thoracic specialist radiologist (D.G.M.) blinded to the subject group using a modified Bhalla scoring system as previously described.¹² Both inspiratory and expiratory scans were scored. Each of six lobes was scored (the lingula was regarded as a separate lobe) at inspiratory CT scanning, as previously described,¹³ using a modification of the Bhalla system.¹⁴ Air trapping was evaluated. The presence and extent of bronchiectasis, on the basis of established CT criteria,^{15,16} were scored as follows: grade 0 = no disease; grade 1 = localised bronchiectasis affecting one or part of one bronchopulmonary segment (localised); grade 2 = bronchiectasis in more than one bronchopulmonary segment (extensive); grade 3 = generalised cystic bronchiectasis. The average severity of bronchial dilatation was quantified relative to the adjacent pulmonary arteries as follows: grade 0 = no bronchiectasis; grade 1 = 100 – 200% arterial diameter; grade 2 = 200 – 300% arterial diameter; grade 3 = $>300\%$ arterial diameter. Bronchial wall thickness was quantified relative to the adjacent pulmonary arteries as follows: grade 0 = none; grade 1 = $<50\%$ arterial diameter; grade 2 = 50 – 100% arterial diameter; grade 3 = $>100\%$ arterial diameter. The presence or absence of mucus within the large airways and (separately) within the centrilobular bronchioles was recorded.

Sputum induction, processing and cell counts

Sputum induction combined with bronchial provocation testing was performed using ultrasonic nebulisation of 4.5% saline for doubling time periods.¹⁷ Normal (0.9%) saline was used where pre-bronchodilator FEV₁ was <1.5 L. The sputum was selected from saliva and dispersed using dithiothreitol as described previously.¹⁷ The suspension was filtered, and a total cell count (TCC) of leucocytes and viability performed. Cytospins were prepared stained (May–Grunwald Geimsa) and a differential cell count obtained from 400 non-squamous cells. An adequate sputum sample was one that returned a cell count from more than 400 non-squamous cells, and a viability of more than 40%. Determination of IL-8 was by ELISA (R&D Systems, Minneapolis, MN, USA), previously validated for use in induced sputum.¹⁸

Pulmonary function testing

Participants withheld bronchodilators for their duration of action before testing. Three reproducible measurements of FEV₁ and FVC were obtained (KoKo PD Instrumentation, Louisville, CO, USA) before and after inhalation of 200 µg albuterol via a metered dose inhaler with valved holding chamber (Volumatic, Allen and Hanbury's, Melbourne Victoria, Australia) using predicted values according to Knudson et al.¹⁹ The carbon monoxide transfer co-efficient (KCO) was determined according to ATS guidelines (Med-Graphics Elite DX Pulmonary function testing system Medical Graphics Corporation, Minnesota, MN, USA).²⁰

Data analysis

Data were analysed using Stata 9 (Stata Corporation, College Station, Texas, USA). Results are reported as median and interquartile range unless otherwise indicated. Analysis was performed using the two-sample Wilcoxon Rank Sum test and Fishers' exact test for categorical data.

Associations between data were determined using the Spearman rank correlation. Results were reported as significant when $p < 0.05$.

Results

The clinical characteristics of the participants (Table 1) show that the groups were well matched for age and sex. There was expected overlap in some phenotypic features, but each group showed a distinct clinical and physiological profile. The participants with NA and COPD had a similar degree of airflow obstruction and inhaled corticosteroid (ICS) therapy. The participants with NA reported a long duration of asthma (mean 41 years) and an increased prevalence of atopy. Gas diffusion (KCO) was normal and all had airway hyperresponsiveness. In contrast the participants with COPD had a greater smoking history, reduced KCO, a lower dose response to hypertonic saline and a recent diagnosis of airway disease (mean 4 years). The SC resembled the COPD group in numbers of smokers and exsmokers, with significantly fewer pack years and a similar low prevalence of atopy. They had normal FEV₁, no diagnosed airway disease, no airways hyperresponsiveness and no ICS use.

The inflammatory markers from induced sputum (Table 2) identified a prominent neutrophilic bronchitis in NA and COPD. The NA group had the highest values for total cell count, neutrophil percentage and IL-8, and the COPD group was intermediate between NA and SC. When compared to NA and COPD, the SC group had a lower IL-8 level, and an increased proportion of bronchial epithelial cells.

There were distinct differences in the pattern of HRCT changes (Table 3). NA had more extensive airway disease, with increased bronchial wall thickening (Fig. 1) and minimal emphysema. In contrast, the COPD and SC groups had significantly less bronchial wall thickening and the COPD group had more extensive emphysema. None of the SC group had significant bronchial wall thickening on HRCT.

Table 1 Clinical and Physiological features of participants with neutrophilic asthma (NA), chronic obstructive pulmonary disease (COPD) and smoking controls (Controls).

	Neutrophilic asthma	COPD	Controls	<i>p</i>
<i>N</i>	10	17	8	
Age, years mean (SD)	65 (10)	68 (7)	62 (12)	0.214
Gender, male	5	12	6	0.523
Atopy, <i>n</i> (%)	9 (90)	8 (47)	3 (38)	0.039
Smoker, never ex current	4 6 0	0 15 2†	0 4 4†	0.001
Pack years median (IQR)	21.5 (0.4–40)#	67.5 (38.8–75)	34.4 (13.0–39.8)#	0.035
Duration of airway disease median (IQR)	41.5 (26–47)	4 (2–7)	—	<0.001
FEV ₁ % predicted, mean (SD)	62.1 (22.1)	63.8 (16.7)	100.1 (9.9)#,†	0.001
FEV ₁ : FVC %, mean (SD)	61.2 (11.2)	57.6 (8.0)	76.8 (4.7)#,†	0.001
KCO % predicted, mean (SD)	97.0 (13.5)#	56.5 (16.5)	73.1 (14.8)	<0.001
AHR present <i>n</i> (%)	8 (100)	11 (48), <i>n</i> = 16	0 (0)†#	<0.001
Dose response slope, median (IQR)	2.9 (2.2–12.8)#	1.1 (0.7–2)	0.16 (0.06–0.32)†#	<0.001
ICS ^a µg/day, median (IQR)	1800 (800–2000)	2000 (2000–2000) <i>n</i> = 11	—	0.402

$p < 0.017$ vs. COPD † $p < 0.017$ vs. NA.

^a ICS dose is calculated a 1 µg of beclomethasone = 1 µg budesonide = 0.5 µg fluticasone.

Table 2 Induced sputum inflammatory markers in neutrophilic asthma (NA), chronic obstructive pulmonary disease (COPD) and smoking controls (Controls). All data are median (IQR).

	Neutrophilic asthma	COPD	Controls	<i>p</i>
Total cell count $\times 10^6/\text{mL}$	8.7 (6.6–10.0)	5.1 (3.5–8.6)	3.1 (1.4–5.0)†	0.022
Viability, %	88 (84–93)	90 (77–92)	80 (60–88)	0.223
Neutrophils, %	77.3 (70.1–97.1)#	61.0 (53.5–73.5)	43.3 (20–58.1)†	0.002
Eosinophils, %	1.3 (0.3–2.3)	0.5 (0.3–1.5)	0.3 (0.1–0.4)	0.181
Macrophages, %	19.5 (15.3–24.3)	32.5 (9.5–41.3)	51.9 (33.9–70.9)†	0.008
Lymphocytes, %	0.1 (0.0–0.5)	0.8 (0.3–1.0)	0.8 (0.1–1.6)	0.125
Columnar epithelials, %	0 (0–0.3)#	1 (0.5–2.0)	3.8 (2.0–7.5)†#	<0.001
Squamous, %	2.0 (0–3.4)	1.7 (0.5–6.1)	7.0 (1.1–9.6)	0.242
IL-8 ng/mL	41.8 (14.4–75.5)	16.7 (9.9–21.3)	5.1 (2.3–7.3)†#	0.004

#*p* < 0.017 vs. COPD †*p* < 0.017 vs. NA.

Correlations

There were important correlations observed between physiological and inflammatory parameters and HRCT scores. FEV₁% predicted was significantly associated with the degree of bronchial wall thickness, $r = -0.443$, $p = 0.008$ (Fig. 2) and chest consolidation ($r = -0.409$, $p = 0.015$) and total lung score ($r = -0.454$, $p = 0.006$). As expected, KCO% predicted was significantly related to total emphysema score, $r = -0.656$, $p < 0.001$. Induced sputum neutrophils were significantly associated with a number of clinical parameters including disease duration ($r = 0.479$, $p = 0.011$) and both neutrophils and IL-8 were negatively associated with the degree of airflow obstruction (FEV/VC, Neutrophils: $r = -0.375$, $p = 0.027$, IL-8: $r = -0.532$, $p = 0.002$; and FEV₁% predicted, Neutrophils: $r = -0.431$, $p = 0.010$, IL-8: $r = -0.644$, $p < 0.001$). Neutrophils and IL-8 were also related to bronchial wall thickness ($r = 0.394$, $p = 0.019$ and $r = 0.406$, $p = 0.024$ respectively) but not with emphysema ($r = -0.01$, $p = 0.938$ and $r = 0.058$, $p = 0.755$).

Discussion

This study has demonstrated for the first time that the pattern of radiographic change from whole lung HRCT differs between neutrophilic asthma and COPD, further confirming that neutrophilic asthma represents a distinct phenotype of inflammatory airway disease. Abnormal

bronchial wall thickness is a well-described CT feature of asthma and was seen in the neutrophilic asthma group, where the amount of bronchial wall thickness was significantly greater than in the COPD or smoking control groups. In contrast, emphysema was greatest in the COPD group, and not recorded as a feature of neutrophilic asthma. FEV₁% predicted was negatively associated with bronchial wall thickening, while KCO% predicted was negatively associated with the total emphysema score. Bronchiectasis was minimal in all groups. These data show that the pattern of radiographic lung abnormality in neutrophilic asthma is significantly different from COPD, indicating that neutrophilic asthma is a distinct inflammatory subtype of asthma with a different pathogenesis to COPD.

HRCT in asthma

While HRCT has been studied extensively in asthma, the HRCT changes associated with distinct inflammatory phenotypes have not been reported previously. The range of observed abnormalities in asthma includes bronchial wall thickening, emphysema, bronchiectasis, consolidation, pneumomediastinum, atelectasis and mosaic lung attenuation.⁷ In addition, dynamic HRCT shows variability in the distribution of ventilation,²¹ treatment responsive changes in lung attenuation, and altered airway distensibility in asthma.^{21–23} More severe forms of asthma are associated with bronchial wall thickening,²⁴ focal hyperlucency, centrilobular opacity, and bronchiectasis.

Table 3 HRCT changes in neutrophilic asthma, chronic obstructive pulmonary disease (COPD) and smoking controls (controls). Data are median (IQR), or *n* (%).

	Neutrophilic asthma	COPD	Controls	<i>p</i>
Bronchial wall thickness score	7 (4–8)	4 (3–6)†	3.5 (2.5–5)†	0.031
Bronchial walls >50% arterial diameter, <i>n</i> (%)	7 (70)	1 (6)†	0 (0)†	<0.001
Mucus plugs present, <i>n</i> (%)	5 (50)	3 (18)	2 (20)	0.211
Total emphysema score	0 (0–0)	60 (0–140)†	5 (0–10)	0.004
Extent of bronchiectasis score	0 (0–5)	0 (0–1)	0.5 (0–1)	0.899
Severity of bronchiectasis score	0 (0–3)	0 (0–1)	0.5 (0–1)	0.903
Decreased attenuation score	15 (10–135)	20 (5–30)	7.5 (0–55)	0.443
Number of lobes with decreased attenuation	3 (2–6)	2 (1–3)	1 (0–5)	0.267
Total lung score	8.5 (4–19)	6 (4–7)	4.5 (3–8)	0.214

†*p* < 0.017 vs. NA.

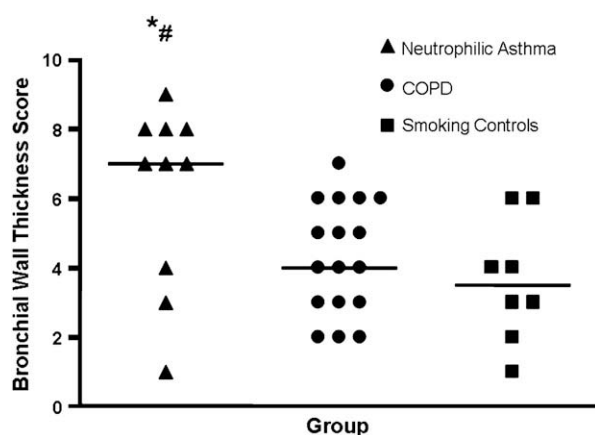


Figure 1 Bronchial wall thickness score for participants with neutrophilic asthma, COPD and smoking controls. Horizontal bar represents the median result. Across group p -value $p = 0.031$. * $p = 0.008$ vs. smoking controls # $p = 0.017$ vs. COPD.

Several studies have sought to identify HRCT changes in different subtypes of asthma. In asthma the development of persistent airflow obstruction was associated with increased bronchial wall thickening on HRCT.^{25,26} Bronchial wall thickening is the most prominent abnormality reported in asthma. It is considered to be due to submucosal oedema, inflammation, and airway wall fibrosis, and to be potentially reversible.²⁷ Inhaled corticosteroid and long-acting beta-agonist therapy were observed to reduce bronchial wall thickening²⁸ on HRCT, and these changes correlated with reduced thickness of the reticular basement membrane and mucosal eosinophils on bronchial biopsy. Bronchial wall thickening was also related to increasing asthma severity,²⁴ and is prominent in near fatal cases of asthma.²⁹ Airway wall thickening is likely to be a major determinant of airflow obstruction in asthma and bronchiectasis,^{29–31} since it correlates with FEV₁ in these conditions.^{32,33} In this study we also found that the degree of bronchial wall thickening was significantly correlated with airflow obstruction.

Changes in an eosinophilic asthma inflammatory subtype

The HRCT findings in asthma with eosinophilic inflammation have been compared to nonasthmatic eosinophilic bronchitis (NAEB).³⁴ The patients with eosinophilic airway diseases (asthma, NAEB) had a similar pattern of HRCT changes with increased bronchial wall thickening, centrilobular prominence and air trapping. Inflammatory cell activation and airway remodelling were found to be related to HRCT changes in asthma,³⁵ suggesting that airway inflammation in asthma is associated with the extent of airway abnormalities on HRCT, with eosinophilic inflammation specifically associated with bronchial wall thickening. Our data extend these findings to show that neutrophilic inflammation in asthma is also associated with abnormal bronchial wall thickening. Together these data suggest that it is the presence, location and possibly severity of inflammation in asthma that is associated with

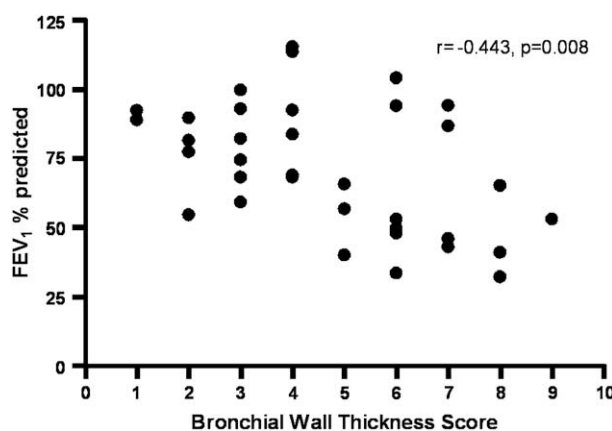


Figure 2 Relationship between bronchial wall thickness score and FEV₁% predicted in all participants.

bronchial wall thickening on HRCT, rather than the specific inflammatory cell pattern (i.e. eosinophil vs. neutrophil) that is present. This is further supported by the data of Wark et al., who studied asthma complicated by allergic bronchopulmonary aspergillosis where there is a mixed eosinophil and neutrophil inflammatory patterns.³⁶ These authors found that both the eosinophil (ECP) and neutrophil (MPO) activation markers from induced sputum were correlated with the extent of HRCT abnormalities.

Bronchial wall thickening in COPD

Inflammatory changes in the small airways due to airway inflammation have also been identified as an important pathological abnormality in COPD that is associated with disease progression.⁸ A recent HRCT study suggests that bronchial wall thickening and emphysema have distinct and separate inheritance patterns in COPD⁹ and that COPD can be further subtyped based on the presence of emphysema and/or bronchial wall thickening.³⁷ Airway wall thickening is related to the degree of airway obstruction in COPD,³⁸ to cumulative smoking history and to airway inflammation with increase in both sputum eosinophils³⁷ and neutrophils.³⁹ When HRCT changes in asthma and COPD are compared²⁵ the parenchymal abnormalities are more prevalent in COPD, whereas bronchial wall thickening is more prevalent in asthma compared with COPD. These results concur with the results of our study where we found that the extent of bronchial wall thickening was significantly greater in neutrophilic asthma than in COPD and smoking controls, but that parenchymal changes were greater in COPD. Participants with neutrophilic asthma had a longer duration of disease compared to participants with COPD. It would be interesting in further research to investigate if the degree of bronchial wall thickness is related to duration of disease.

Other CT changes

Bronchial dilation is another HRCT finding observed in asthma but is not related to sputum inflammatory markers or remodelling parameters in asthma.⁴⁰ In bronchiectasis,

bronchial dilation did not correlate to the degree of airflow obstruction, and may possibly protect against airflow obstruction in bronchiectasis.¹² Consequently, it is not surprising that this HRCT abnormality is not related to airway inflammation in asthma.

Emphysema and bronchiectasis are uncommon in asthma. In the present study emphysema was not seen in the participants with neutrophilic asthma, and when present, emphysema was associated with smoking, being present in both COPD and in smoking controls. Emphysema is now recognised to occur in up to 33% of asymptomatic smokers,⁴¹ consistent with our observations. In COPD, Patel et al. found evidence of bronchiectasis on HRCT⁴² which was associated with increased inflammatory markers, bacterial colonization and more severe COPD exacerbations. In this study, the extent of bronchiectasis was minimal in all cases.

Conclusions

This study has demonstrated significant radiological abnormalities in neutrophilic asthma, the most prominent of which is bronchial wall thickening. The pattern of radiographic change in neutrophilic asthma was different to both COPD and smokers without diagnosed airway disease. This means that although the neutrophilic inflammatory pattern may be similar in these airway conditions, neutrophilic asthma is distinct from COPD in that it is a dominant airway (and not parenchymal) disease where there is an intense neutrophilic bronchitis and probably bronchiolitis. The results support consideration of neutrophilic asthma as a distinct asthma subtype, which is associated with innate immune dysfunction and potentially requires identification of different treatment approaches.

Conflict of interest statement

Dr. Simpson, Professor Gibson and Dr. Milne have no conflict of interest to disclose.

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